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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,763	AKHAVAN-TAFTI ET AL.	
	Examiner	Art Unit	
	Stephanie K. Mummert, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/15/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on June 15, 2006 is acknowledged and has been entered. Claims 1-4, 42-43, 47 and 50 have been amended. Claims 1-50 are pending.

Claims 1-50 are discussed in this Office action.

Response to Arguments

1. Applicant's arguments, see p. 1, filed June 15, 2006, with respect to the rejection(s) of claim(s) 2 and 49 under 35 U.S.C. 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Seligson in view of Summerton, with clarification provided regarding the prima facie case for obviousness. Additionally, these references have been applied to claims 1-3, 6-12, 19-22, 30, 32-35, 42-46, 48 and 50 as amended.

2. Applicant's arguments, see p. 2, with respect to the rejection(s) of claim(s) 3-5 under 35 U.S.C. 103 as being unpatentable over Summerton in view of Seligson as noted above and further in view of Platz and Hatekayama have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Bronstein and Goshe.

3. Applicant's arguments, see p. 5 with respect to the rejection(s) of claim(s) 13-15 and 23-29 under 35 U.S.C. as being unpatentable over Summerton in view of Schaap have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Seligson in view of

Summerton and further in view of Schaap, with clarification provided regarding the prima facie case for obviousness.

Regarding Applicant's request for an English Translation of Mukhamedgaliev, please see the translation attached, which is discussed in more detail below.

4. All of the remaining amendments and arguments have been thoroughly reviewed and considered but are moot in view of the new grounds of rejection stated below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL.

NEW GROUNDS OF REJECTIONS

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on June 15, 2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

1. Claims 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seligson et al. (US Patent 4,935,342; January 1990) in view of Summerton et al. (US Patent 6,060,246; May 2000). Seligson teaches a method of separation, isolation and purification of DNA or RNA from biological samples using quaternary ammonium groups for binding (col. 3, lines 56-66, where beds of anion exchange material are used; see also Table found under col. 5/6, where specific types of anion exchange materials are described in detail, with specific notice of QMA and QAE columns, which contain quaternary ammonium groups).

With regard to claim 1, Seligson teaches a method of isolating a nucleic acid from a sample comprising:

a) providing a solid phase comprising a matrix selected from silica, glass, insoluble synthetic polymers, and insoluble polysaccharides (col. 5, lines 22-27 and 31-36, where the anion exchangers comprise silica glass, vinyl polymers, or agarose); a nucleic acid binding portion for attracting and non-sequence-specific binding of nucleic acids, wherein the nucleic acid binding portion of the solid phase is selected from a ternary sulfonium group of the formula SR2+X- where R is selected from C1-C20 alkyl, aralkyl and aryl groups, a quaternary ammonium group of formula NR3+X- wherein R is selected from C1-C20 alkyl, aralkyl and aryl groups, and a quaternary phosphonium group PR3+X- wherein R is selected from C1-C20 alkyl, aralkyl and aryl groups, and where X is an anion (col. 5, lines 1-65, specifically lines 33-37 and 56-65, where the quaternary group is usually dimethylammonium or trimethylammonium and where the anion is chloride);

b) combining the solid phase with the sample containing the nucleic acid to bind the nucleic acid to the solid phase (col. 6, lines 13-20, where DNA or RNA to be examined are loaded on experimental columns in a salt low enough to assure efficient binding; see also col. 11, Example I, lines 10-12);

c) separating the sample from the solid phase and e) releasing the nucleic acid from the solid phase (col. 11, Example I, lines 21-27, where the nucleic acids are eluted from the support).

With regard to claim 2, Seligson also teaches that the nucleic acid binding portion comprises a quaternary ammonium group NR3+X, wherein R is selected from alkyl and wherein X is an anion (col. 5, lines 1-65, specifically lines 33-37 and 56-65, where the quaternary group is usually dimethylammonium or trimethylammonium and where the anion is chloride).

With regard to claim 3, Seligson teaches an embodiment of claim 1, wherein the nucleic acid binding portion is a quaternary ammonium group and the R groups each contain from 4-20 carbons (col. 5, lines 1-65, specifically lines 33-37 and 56-65, where the quaternary group is usually dimethylammonium or trimethylammonium and where the anion is chloride).

With regard to claim 6 and 9-10, Seligson teaches an embodiment of claim 1, wherein the solid support portion is selected from particles, microparticles and beads (col. 5, lines 13-15, where the exchangers are supplied as spherical or irregular granules), glass or silica (col. 5, lines 22-27 and 31-36, where the anion exchangers comprise silica glass).

With regard to claim 7, Seligson teaches an embodiment of claim 1, wherein the solid support portion comprises an insoluble synthetic polymer (col. 5, lines 22-27 and 31-36, where the anion exchangers comprise vinyl polymers).

With regard to claim 44, Seligson teaches an embodiment of claim 1, further comprising, after step b) washing the solid phase having captured nucleic acid bound thereto with a wash solution to remove other components of the sample from the solid phase (col. 11, Example I, lines 14-19, where the column is washed to remove mucopolysaccharides and proteins).

With regard to claim 48 and 49, Seligson teaches an embodiment of claim 1 and 2 further comprising: a) releasing the nucleic acid from the solid phase in step e) into a solution; and b) using the solution containing the released nucleic acids directly in a downstream process (col. 14, lines 16-24); and b) using the solution containing the released nucleic acid directly in a downstream process (col. 14, lines 16-24).

Regarding claim 1 and 2, Seligson does not teach the limitation that the solid phase comprises a cleavable linker portion or cleaving the cleavable linker portion.

Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

With regard to claim 1, Summerton teaches and a cleavable linker portion linking the nucleic acid binding portion to the solid support (col. 7, lines 15-17 and col. 8, line 64 to col. Col. 9, line 42, where the cleavable linker can include disulfide, esters, orthonitrobenzyl esters, peptides and oligosaccharides); and

d) cleaving the cleavable linker (col. 12, lines 19-28); and

With regard to claim 2, Summerton teaches cleaving the linker thereby separates the nucleic acid from the solid phase (col. 12, lines 19-28 or lines lines 29-36).

With regard to claim 8, Summerton teaches an embodiment of claim 7, wherein the polymer is selected from polystyrene and polyacrylic polymers (col. 18, lines 54-56, where the microparticles comprise polystyrene).

With regard to claim 11, Summerton teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase further comprises one or more connecting portions (col. 9, lines 38-42, where a spacer group or additional linkage groups can connect the capture component to the reagent surface).

With regard to claim 12, Summerton teaches an embodiment of claim 1, wherein the solid phase further comprises a magnetically responsive portion (col. 5, lines 13-60, where glass beads, or beads with polyethylene glycol linkages to reduce binding of undesirable components, and the use of magnetic particles are discussed; see also col. 18, lines 34-55).

With regard to claim 19, Summerton teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase is cleaved reductively (col. 9, lines 28-31, where the disulfide is cleaved with a sulfhydryl).

With regard to claim 20, Summerton teaches an embodiment of claim 19, wherein the cleavable linker comprises a disulfide group (col. 2, lines 41-43; see also col. 9, lines 28-31).

With regard to claim 21, Summerton teaches an embodiment of claim 19, wherein the reductive cleavage is performed with a reducing agent selected from thiols, amines and phosphines. (col. 9, lines 28-31, where the disulfide is cleaved with a sulfhydryl).

With regard to claim 22, Summerton teaches an embodiment of claim 21, wherein the reducing agent is selected from 2-mercaptoethanol or dithiothreitol (col. 9, lines 28-31).

With regard to claim 30, Summerton teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase is cleaved enzymatically (col. 9, lines 28-37, where the enzymes disclosed include esterases, peptidases, proteases, oligosaccharidases, glycosidases).

With regard to claim 32, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises an ester which is cleaved by hydrolase enzyme (col. 2, lines 41-45; see also col. 9, lines 28-37).

With regard to claim 33, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises an amide which is cleaved by a protease enyme (col. 9, lines 28-37, where peptides are cleaved by peptidases or proteases).

With regard to claim 34, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises a peptide which is cleaved by a peptidase (col. 2, lines 41-45; see also col. 9, lines 28-37, where peptides are cleaved by peptidases or proteases).

With regard to claim 35, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises a glycoside which is cleaved by a glycosidase (col. 2, lines 41-45; see also col. 9, lines 28-37, where oligosaccharides are cleaved by glycosidases).

With regard to claim 42, Summerton teaches an embodiment of claim 1, wherein the cleaving and releasing steps are performed as sequential steps using separate and distinct solutions to accomplish each step (col. 5, lines 1-7, where non-target polynucleotides are released through cleavage of linkers, followed by elution of target molecules in a subsequent step).

With regard to claim 43, Summerton teaches an embodiment of claim 1, wherein the cleaving and releasing steps can be performed together in the same step (col. 6, lines 58-64, where a strongly basic amine is used in the capture component and bound molecules are released by selective cleavage of the linkage instead of through elution with adjustments to pH of solutions).

With regard to claim 45, Summerton teaches an embodiment of claim 1, wherein the step of separating the sample from the solid phase is accomplished by magnetic separation (col. 18, lines 64 to col. 19, line 17, where magnetic separation was used in the isolation of poly-A tailed alpha globin RNA).

With regard to claim 46, Summerton teaches an embodiment of claim 1, wherein the step of separating the sample from the solid phase is accomplished by a process selected from centrifugation and vacuum aspiration (col. 19, lines 8-11, where supernatant was aspirated).

With regard to claim 50, Summerton teaches an embodiment of claim 48, wherein the solution containing the released nucleic acid is used directly in a nucleic acid amplification reaction whereby the amount of the nucleic acid or segment thereof is amplified using a polymerase or ligase-mediated reaction (col. 14, lines 16-24).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the cleavable linkers taught by Summerton into the isolation technique taught by Seligson. As taught by Seligson, prior art techniques for isolation of DNA/RNA do "not provide adequately isolated nucleic acids needed for hybridization assays in a clinical laboratory. Contaminates in the biological samples interfere with fixing DNA/RNA hybridization and detection. As a consequence, to provide useful clinical hybridization assays,

there exists a need for rapid methods to obtain hybridization nucleic acids from biological samples" (col. 2, lines 10-20). To this end, Seligson teaches isolation and purification of nucleic acids using solid phase binding of nucleic acids to anion exchangers, including quaternary ammonium groups. However, Seligson does not teach the inclusion of a solid phase which comprises a cleavable linker portion.

As taught by Summerton, "the present invention, by combining rapid capture and concentration of polynucleotides with selective targeting of analyte molecules greatly enhances this process" in contrast to the "generally very slow and inefficient, especially for low-copy sequences" process of conventional hybridization to sequence-specific probes (col. 14, lines 4-15). One of ordinary skill in the art at the time the invention was made would have recognized the benefit of enhanced and rapid isolation of nucleic acid molecules. While it is noted that the instant invention is directed to initial non-sequence specific isolation of nucleic acids, and Summerton teaches an ultimate focus on sequence-specific target nucleic acids, the process taught by Summerton incorporates two binding molecules on the surface of the solid support - a capture component, which "binds nucleic acids, or a subset of nucleic acids, in a rapid but non-specific manner" and a target-specific probe, which provides sequence specific binding of target analytes (col. 4, lines 18-40; see also Figure 1). The cleavable linker provides that "non-specific nucleotides are selectively released from the capture component following probe-target pairing, preferably via cleavage of linkers, to leave only analyte or target sequence bound to the rapid-pairing reagent" (col. 5, lines 1-5).

Considering that Seligson is directed to obtaining hybridization nucleic acids from biological samples, the inclusion of the cleavable linker provided by Summerton provides for a

more rapid release of polynucleotides which bind non-specifically to the capture component of the 'rapid pairing reagent' taught by Summerton. While the additional teachings of Summerton, including the retention of target sequences, prior to elution, may be of interest in further extensions of the teachings of Seligson, particularly as it relates to the specific hybridization assays noted previously, based solely on the additional benefit provided by the cleavable linker taught by Summerton for elution of non-sequence specifically bound nucleic acids, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the cleavable linkers taught by Summerton into the method of isolation taught by Seligson with a reasonable expectation for success.

2. Claims 3-5 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seligson in view of Summerton as applied to claim 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 above and further in view of Bronstein et al. (US Patent 6,602,657; August 2003) and further in view of Goshe et al. (US Patent 6,818,454; November 2004). Seligson in view of Summerton teaches the limitations of claims 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 as recited in the 103 rejection stated above. Neither Seligson or Summerton teach of the use of quaternary phosphonium or ternary sulfonium groups for binding of nucleic acids, however amine groups are discussed.

In addition to the quaternary ammonium taught by Seligson, Bronstein teaches a method of measuring the activity of at least two reporter gene products, including a water soluble polymeric enhancer molecule to enhance the light signal (Abstract, col. 4, lines 5-20).

With regard to claim 3, Bronstein in view of Seligson teaches an embodiment of claim 1, wherein the nucleic acid binding portion is a quaternary ammonium group and the R groups each contain from 4-20 carbons (col. 4, lines 5-20; col. 11, line 26-44 and line 63 to col. 12, line 19, where the polymeric structures include quaternary ammonium salts; and where the R group contain a 1-20 carbons).

With regard to claim 4, Bronstein in view of Summerton and Seligson teaches an embodiment of claim 1 wherein the solid phase is selected from a quaternary phosphonium group PR3+X- wherein R is selected from C1-C20 alkyl, aralkyl, and aryl groups, and wherein X is an anion (col. 4, lines 5-20; col. 11, line 26-44 and line 63 to col. 12, line 19, where the polymeric structures include posphonium salts; and where the R group contain a 1-20 carbons).

With regard to claim 5, Bronstein teaches an embodiment of claim 4, wherein each R group of the solid phase is a butyl group (col. 4, lines 5-20; col. 11, line 26-44 and line 63 to col. 12, line 19, where the polymeric structures include posphonium salts; and where the R group contain a 1-20 carbons).

With regard to claim 47, Bronstein teaches an embodiment of claim 1, wherein the nucleic acid binding portion of the solid phase is a ternary sulfonium group of the formula SR2+X- where R is selected from C1-C20 alkyl, aralkyl and aryl groups, and wherein X is an anion (col. 4, lines 5-20; col. 11, line 26-44 and line 63 to col. 12, line 19, where the polymeric structures include sulfonium salts; and where the R group contain a 1-20 carbons).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute a ternary phosphonium group or a ternary sulfonium group for the quaternary ammonium group taught by Seligson. As taught by Bronstein, the inclusion of an

ammonium or phosphonium groups as part of synthetic oligomeric or polymeric enhancer substances (col. 11, 63-66), in the method taught by Bronstein "enhances the light signal produced by enzymatic degradation of the dioxetane" (col. 4, lines 5-8). While Bronstein does not teach the inclusion of these groups in the binding of nucleic acids, Brontein does teach an equivalence between quaternary onium groups, including ammonium, phosphonium and sulfonium. Further, as taught by Goshe, ammonium, phosphonium or sulfonium groups retain their charge (col. 9, lines 59-62). The maintenance of the charge of these groups allows for these groups to have non-specific affinity for nucleic acids in solution. The benefit of improved affinity for nucleic acids to a particular solid phase would have been obvious to one of ordinary skill in the art who would therefore have been motivated to include a phosphonium or sulfonium group where quaternary ammonium groups have been used in the past with a reasonable expectation of success.

3. Claim 13-15 and 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Summerton in view of Schaap et al. (US Patent 5,707,559; January 1998). Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

Summerton does not explicitly teach the inclusion of dioxetane linkages as a part of the invention disclosed as recited in the 102 rejection stated above, but Summerton does teach the inclusion of cleavable linkages of a variety of forms in the isolation of target nucleic acids. Schaap teaches novel light-producing compounds termed 1,2-dioxetanes which can be triggered to produce light at room temperature (Abstract).

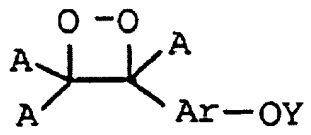
With regard to claim 13, Schaap teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase is cleaved hydrolytically (col. 26, lines 54-65, where the base is potassium hydroxide; col. 27, lines 44-46, where the proof of enzyme-catalyzed hydrolysis begins).

With regard to claim 14, Schaap teaches an embodiment of claim 13, wherein the hydrolytic cleavage is performed with a solution that contains a base selected from hydroxide and alkoxide salts (col. 26, lines 54-65, where the base is potassium hydroxide).

With regard to claim 15, Schaap teaches an embodiment of claim 14, wherein the base is selected from hydroxide salts and alkoxide salts (col. 26, lines 54-65, where the base is potassium hydroxide).

With regard to claim 23, Schaap teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase comprises a triggerable dioxetane ring which is cleaved by a triggering agent (Abstract, see also col. 26, lines 40-65).

With regard to claim 24, Schaap teaches an embodiment of claim 23, wherein the triggerable dioxetane has the formula



wherein the group A represent stabilizing substituents selected from alkyl, cycloalkyl, aryl, aryloxy, and alkoxy (col. 6, lines 43-65, where A, or R1, R3 and R4, is selected from alkyl, alkoxy, aryloxy, and spirofused aryl groups), Ar represents an aryl ring group which can contain additional substituents selected from halogens, alkoxy and amine groups (col. 6, lines 43-65, where R2 is an aryl which can include oxy groups), Y is a group or atom which is removable by

a triggering agent selected from the chemical agents and enzymes to cause fragmentation of the dioxetane ring (col. 6, line 43 to col. 7, line 25, wherein OY is an oxy group substituted on an aryl ring which forms an unstable oxide intermediate 1,2-dioxetane compound when triggered to remove Y by an activating agent).

With regard to claim 25, Schaap teaches an embodiment of claim 24, wherein the OY group is selected from OH, $OSiR^3_3$, wherein R^3 is selected from alkyl and aryl groups, carboxyl groups, phosphate salts sulfate salts and glycoside groups (col. 8, lines 3-12, where OY can be hydroxyl, aryl siloxy and oxygen pyranoside, for example).

With regard to claim 26, Schaap teaches an embodiment of claim 24, wherein Ar in the triggerable dioxetane is a substituted or unsubstituted phenyl or napthyl group (col. 8, lines 3-12, where Ar or R2 is an aryl group that can be a phenyl, biphenyl, fused phenyl and other aryl groups that can contain between 6 and 30 carbon atoms and can include other substituents).

With regard to claim 27, Schaap teaches an embodiment of claim 23, wherein the triggering agent is selected from bases, fluoride ion, a esterase, a phosphatase, a sulfatase, and a glycosidase (col. 26, lines 40- col. 27, lines 28-66, where the triggering agent is selected from bases, fluoride ion and see col. 40; see also col. 8, lines 28-39, where additional triggering agents acids, bases, salts and enymes).

With regard to claim 28, Schaap teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase comprises an electron rich alkene, which is cleaved by conversion to a thermally unstable dioxetane (col. 8, lines 49-67).

With regard to claim 29, Schaap teaches an embodiment of claim 28, wherein the alkene is converted to the unstable dioxetane by reaction with a singlet oxygen (col. 8, lines 49-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the dioxetane compound taught by Schaap into the DNA binding compound which incorporated cleavable linkers in the isolation of target nucleic acid molecules as taught by a combination of Seligson and Summerton. As taught by Schaap, the dioxetane compound is a "novel stable 1,2-dioxetanes which can be decomposed with an activating agent to form light and two carbonyl compounds" and furthermore, a compound that is stable at room temperature for an extended period of time, that is activatable by chemical and biochemical means, and which can generate light (col. 5, lines 22-34). At the time the invention of Schaap was made, dioxetane compounds were known to be capable of chemiluminescence, but the compounds were unstable or needed to be reacted under conditions unfavorable to evaluation of biological macromolecules (col. 1-3). With the improvements made with the synthesis of the compound taught by Schaap, the dioxetane compound provides a stable compound, capable of being cleaved by enzymatic or chemical means and yields stable fluorescence. The target nucleic acid isolation technique taught by Summerton has an embodiment directed to the isolation of non-specific and specific target nucleic acids. Summerton teaches the use of multiple types of linkers to connect the different capture portions of the solid phase and it would have been obvious to include another variation, particularly one as versatile as the dioxetane compound taught by Schaap. One of ordinary skill in the art would have recognized the benefit of luminescence upon cleavage of a cleavable linkage used in the isolation of nucleic acids, and the additional benefits of a thermally stable chemical linkage capable of enzymatic or chemical cleavage. As noted by Seligson, during the analysis of the nucleic acid isolated through the technique, "typical analysis of the nucleic acids include

spectrophotometric scans (210 nm → 300 nm), comparison of 260 nm/ 280 nm absorbance ratios, and 230 nm/ 26O nm absorbance ratios for purity and concentrate" and "fluorescent scans may be used to detect containment fluorescence and DNA hybridization tests are done to determine the presence of intact target regions of the collected DNA" (col. 11, lines 30-40). Luminescence upon cleavage would have provided an additional method of detecting cleavage of the non-specifically bound nucleic acids from the capture agent, and would have provided an additional method for detection and analysis of the released nucleic acids. Therefore one of ordinary skill would therefore have been motivated to incorporate the dioxetane compound as an additional type of cleavable linker, in addition to those specifically taught by Summerton, with a reasonable expectation of success.

4. Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seligson in view of Summerton as applied to claims 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 above and further in view of Singh et al. (US Patent 6,514,700; February 2003). Seligson in view of Summerton teach the limitations of claims 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 as recited in the 103 rejection stated above. Neither Summerton or Seligson teaches hydrolytic cleavage in a solution that contains hydrogen peroxide.

Regarding claim 16, Singh teaches a method wherein the hydrolytic cleavage is performed with a solution that also contains hydrogen peroxide (col. 9, lines 26-37, where hydrogen peroxide is used in oxidative cleavage of the linker).

Regarding claim 17, Singh teaches a method wherein the hydrolytic cleavage is performed with a solution that contains a mineral acid (col. 9, lines 10-15, where HCl is included in a cleavage reaction).

It would have been prima facie obvious to one of ordinary skill in the art to substitute hydrogen peroxide and mineral acid for the base or enzymatic cleavage taught by Summerton. It is standard in the art to adjust reaction conditions to achieve the most efficient combination of solvents or reagents appropriate to the specific experiment being conducted. As taught by Singh, there are multiple options for cleavage of a linkage, including, but not limited to "silyl groups being cleaved with fluoride, oxidation, acid bromine or chlorine; o-nitrobenzyl with light; catchecols with cerium salts; sulfides with singlet oxygen or enzyme catalyzed cleavage with hydrogen peroxide" (col. 9, lines 26-37). One of ordinary skill in the art would have recognized the role that routine optimization and substitution of reagents play in the art, who would therefore have been motivated to substitute hydrogen peroxide for the other types of linkages and cleavage options previously taught by Summerton, with a reasonable expectation of success.

5. Claims 36-37 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seligson in view of Summerton as applied to claims 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 above and further in view of Mukhamedgaliev et al. (1994, Uzbekskii Khimicheskii Zhurnal (6), p. 41-3, citations in rejection refer to attached English translation of Russian document) and further in view of Reinecke et al. (Macromol. Rapid Commun., 1996, vol. 17, no. 15-23) and further in view of Bronstein et al. (US Patent 6,602,657; August 2003) and further in view of Goshe et al. (US Patent 6,818,454; November 2004). Summerton teaches methods for rapidly

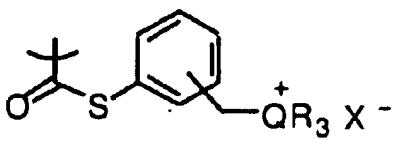
detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

Summerton does not explicitly teach the inclusion of a quaternary phosphonium group as part of the nucleic acid binding portion of their invention, nor does Summerton teach linkage of the phosphonium group to a resin via a thioester linkage as displayed below. Mukhamedgaliev teaches the formation of quaternary phosphonium groups following reaction between methacrylol chloride and triphenylphosphine (p. 1, paragraphs 1-3, where methacryloyl chloride (MAC) was reacted with tri-phenyl phosphine (TPP) and p. 2, bottom paragraph, a polymer that contains quaternary phosphonium groups is formed), which anticipates key components of the formation of the thioester recited in claims 36 and 37 as recited in Example 14 (p. 17 of the specification).

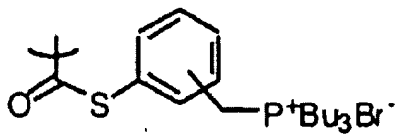
Mukhamedgaliev however, does not explicitly teach the structure of the compound synthesized or the attachment to the polymer using a thioester linkage.

Reinecke teaches a step that would anticipate the step of reacting the resin with 2-mercaptobenyl alcohol as exemplified in Example 14, that is missing from Mukhamedgaliev (Abstract).

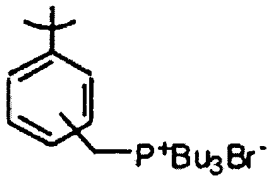
With regard to claim 36, Reinecke in view of Mukhamedgaliev teaches an embodiment which renders obvious a solid phase which comprises a thioester having the formula recited below.



With regard to claim 37, Reinecke in view of Mukhamedgaliev teaches an embodiment which renders obvious a solid phase which comprises a thioester having the formula recited below.



With regard to claim 41, Reinecke in view of Mukhamedgaliev teaches an embodiment which renders obvious a solid phase which comprises a thioester having the formula recited below.



It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to take the various teachings in the art at the time the invention was made, to modify a standard resin to attach a phosphonium group via a thioester linkage. As taught by Reinecke, the use of 2-mercaptobenzyl alcohol, or other aromatic thiols are useful in multi-step reactions, such as the PVC crosslinking analysis taught by Reinecke, because "aromatic thiols can easily substitute chlorine atoms in PVC under Sn2 mechanism, either in solution or melt conditions" and goes on to note further benefits of this type of reaction, including that there are no side reactions due to the high nucleophilicity and low basicity of sulfur (p. 15, paragraph 3).

The benefit of a resin with a phosphonium group attached has been established by previously noted references, including the teaching of the relative equivalence between phosphonium, ammonium and sulfonium groups by Bronstein (col. 4, lines 5-20; col. 11, line 26-44 and line 63 to col. 12, line 19) and the teaching by Goshe that the inclusion of an ammonium or phosphonium group within the support provides a binding group that maintains its charge (col. 9, lines 59-62). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the separate teachings of Summerton, Mukhamedgaliev and Reinecke to arrive at a resin with a phosphonium group attached via a thioester linkage with a reasonable expectation of success.

6. Claims 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seligson in view of Summerton as applied to claims 1-3, 6-10, 12, 19-22, 30, 32-35, 42-46 and 48-50 above and further in view of Hughes et al. (Tetrahedron Letters, 1996, vol. 37, no. 42, p. 7595-7598) and Hagashita et al. (US Patent 4,904,819; February 1999). Seligson in view of Summerton teaches the limitations of claims 1-3, 6-10, 12, 19-22, 30, 32-35, 42-46 and 48-50 as recited in the 103 rejection stated above. However, neither Seligson or Summerton teach a linkage to the solid phase which is an alkylene group bonded to a trivalent phosphonium group, such as trialkylphosnium or triarylphosphonium.

With regard to claim 38, Hughes in view of Summerton teaches an embodiment wherein the cleavable linker portion of the solid phase is an alkylene group of at least one carbon atom bonded to a trialkylphosphonium or triarylphosphonium, nucleic acid binding position and is cleavable by means of a Wittig reaction with a ketone or aldehyde (p. 7596, bottom paragraph,

where the Wittig cleavage of the phosphonium salt to stilbene is described). Hughes does not teach the intricate details of the Wittig reaction as recited in claims 39 and 40. Hagashita teaches the use of a Wittig reaction in the synthesis of bicyclic sulfonamide derivatives (Abstract).

With regard to claim 39, Hagashita teaches an embodiment of claim 38, wherein the Wittig reaction forms a ylide by deprotonation with an alkoxide salt or hydride salt base in an aprotic organic solvent and the ylide reacts with a carbonyl compound selected from aliphatic and aromatic aldehydes and aliphatic and aromatic ketones (col. 6, lines 29-62, where the base treatment includes sodium hydride).

With regard to claim 40, Hagashita teaches an embodiment of claim 39, wherein the solvent is selected from THF, diethyl ether, p-dioxane, DMF and DMSO and the carbonyl compound for reaction with the ylide is acetone (col. 6, line 29 to col. 7, line 15, where tetrahydrofuran or dimethylformamide were noted as a potential solvents and acetone were noted).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the teachings in the art of the inclusion of triphenylphosphine containing compounds attached to a resin, as exemplified by Hughes. As taught by Hughes, "The Wittig reaction of polymer-bound phosphonium salts has been reviewed and has a key advantage that the phosphine oxide by-product remains bound to the polymer and is thus easily separated from the soluble olefinic product by filtration" (p. p. 7595-7596). Hughes also notes that "readily available polymer-supported phosphonium salts can be elaborated with reagents including strong acids, organic bases and reducing agents, and can be cleaved under basic conditions to products lacking polar functionality. The phosphonium linkage thus complements

many existing linkers both in its acid/base stability profile and its cleavage products. This phosphonium linker is currently being exploited for the solid phase synthesis of combinatorial libraries (p. 7597, bottom). The versatility of the triphenyl phosphine compound in reductive reactions would have been obvious to one of ordinary skill in the art who would therefore have been motivated to include the triphenyl phosphine group into the solid phase binding of nucleic acids taught by Summerton with a reasonable expectation of success.

Conclusion

Claim 31 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert, Ph.D. whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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